

## IMMUNOTOXINS WITH INCREASED STABILITY FOR CANCER THERAPY

### SUMMARY

Researchers at the National Cancer Institute's Laboratory of Molecular Biology (NCI LMB) developed and isolated several de-immunized, low toxicity, PE24-based RITs with a longer serum half-life. This was enabled by using a disulfide bond to protect the furin cleavage sequence (FCS). Collectively, the new RITs are designated "DS-PE24" immunotoxins. The NCI seeks parties interested in licensing DS-PE24 RITs.

### REFERENCE NUMBER

E-157-2016

### PRODUCT TYPE

- Therapeutics

### KEYWORDS

- Recombinant Immunotoxin, RIT, Antibody, Mesothelin, Mesothelioma

### COLLABORATION OPPORTUNITY

This invention is available for licensing.

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### DESCRIPTION OF TECHNOLOGY

Recombinant immunotoxins (RITs) are fusions of an antibody-based targeting moiety and a toxin. Pseudomonas exotoxin A (PE) is a bacterial toxin that has been used in several RITs evaluated in clinical trials. Once the Fv portion of the immunotoxin binds to its target receptor, the immunotoxin is internalized by endocytosis. Following internalization, Furin cleavage is critically important for proper cytosolic shuttling of the immunotoxin. Early PE-containing RITs were effective, but also had issues of off-target toxicity.

To mitigate off-target toxicity of PE, the inventors removed specific sequences of domain II, and connected the Fv domain to domain III (PE24) by a furin linker peptide. These PE24-RITs are very active and better tolerated by mice. However, the PE24-containing RITs could potentially be cleaved and inactivated before internalization by cell surface furin or other proteases in the bloodstream or the tumor microenvironment, due to the absence of a key disulfide bond (lost after removal of domain II sequences).

Researchers at the National Cancer Institute's [Laboratory of Molecular Biology](#) (NCI LMB) developed and isolated several de-immunized, low toxicity, PE24-based RITs with a longer serum half-life. This was enabled by using a disulfide bond to protect the furin cleavage sequence (FCS). Collectively, the new RITs are designated "DS-PE24" immunotoxins. The goal of the disulfide bond is to protect the RIT from cleavage-based deactivation before internalization. The most active of these new RITs has longer serum half-life than an RIT without the disulfide bond, has the same anti-tumor activity, while remaining less cytotoxic *in vitro*. Currently, the inventors are working with mouse models to further develop the DS-PE24 RITs towards developing an anti-mesothelin RIT for treatment of mesothelin-expressing cancers, such as mesothelioma.

## POTENTIAL COMMERCIAL APPLICATIONS

- A more stable cancer therapeutic for currently used PE-coupled RITs, for example, anti-mesothelin PE-based immunotoxins

## COMPETITIVE ADVANTAGES

- Protection of the FCS by a disulfide bond results in more stable RIT, which can lead to fewer off-target effects

## INVENTOR(S)

[Ira Pastan M.D.](#) (NCI), et al.

## DEVELOPMENT STAGE

- Pre-clinical (in vivo)

## PUBLICATIONS

Fitzgerald DJ, Kreitman R, et al. [Int J Med Microbiol.](#) 2004;293:577-582; Sampson JH, Akabani G, Archer GE, et al. [J Neurooncol.](#) 2003;65(1):27-35

## PATENT STATUS

- **U.S. Provisional:** US Provisional Patent Application 62/323,668 (NIH Reference E-157-2016/0-US-01), entitled "New, More Stable Immunotoxin Variants with a Disulfide Bond Protecting the Furin Cleavage Site"

## RELATED TECHNOLOGIES

- E-262-2005
- E-292-2007
- E-174-2011
- [E-263-2011 - Increased Therapeutic Effectiveness of PE-Based Immunotoxins](#)

## THERAPEUTIC AREA

- Cancer/Neoplasm